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## ■ ONCOLOGY

# Locally recurrent chondrosarcoma of the pelvis and limbs can only be controlled by wide local excision

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## Aims

The purpose of this study was to investigate the potential for achieving local and systemic control after local recurrence of a chondrosarcoma of bone.

## Patients and Methods

A total of 126 patients with local recurrence (LR) of chondrosarcoma (CS) of the pelvis or a limb bone were identified from a prospectively maintained database, between 1990 and 2015 at the Royal Orthopaedic Hospital, Birmingham, United Kingdom. There were 44 female patients (35%) and 82 male patients (65%) with a mean age at the time of LR of 56 years (13 to 96). The 126 patients represented 24.3% of the total number of patients with a primary CS (519) who had been treated during this period. Clinical data collected at the time of primary tumour and LR included the site (appendicular, extremity, or pelvis); primary and LR tumour size (in centimetres); type of operation at the time of primary or LR (limb-salvage or amputation); surgical margin achieved at resection of the primary tumour and the LR; grade of the primary tumour and the LR; gender; age; and oncological outcomes, including local recurrence-free survival and disease-specific survival. A minimum two years' follow-up and complete histopathology records were available for all patients included in the study.

## Results

For patients without metastases prior to or at the time of local recurrence, the disease-specific survival after local recurrence was 62.5% and 45.5% at one and five years, respectively. After univariable analysis, significant factors predicting disease-specific survival were grade ( $p < 0.001$ ) and surgical margin ( $p = 0.044$ ). After multivariable analysis, grade, increasing age at the time of diagnosis of local recurrence, and a greater time interval from primary surgery to local recurrence were significant factors for disease-specific survival. A secondary local recurrence was seen in 26% of patients. Wide margins were a good predictor of local recurrence-free survival for subsequent recurrences after univariable analysis when compared with intralesional margins ( $p = 0.002$ ) but marginal margins did not reach statistical significance when compared with intralesional margins ( $p = 0.084$ ).

## Conclusion

In cases of local recurrence of a chondrosarcoma of bone, we have shown that if the tumour is non-metastatic at re-staging, an increase in disease-specific survival and in local recurrence-free survival is achievable, but only by resection of the local recurrence with a wide margin.

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Chondrosarcoma (CS) is a malignant neoplasm with cartilage differentiation. It is the second most common primary bone malignancy<sup>1,2</sup> and is classified on its histological grade for cellularity, atypia, and pleomorphism. However, the histological grading is prone to variations in interpretation.<sup>3</sup> This is of importance as CS is resistant

to radiotherapy and conventional chemotherapy; resection, with appropriate margins for the grade of tumour, should be the primary goal.<sup>2,4-6</sup> What constitutes a sufficient margin is debatable. In grade 1 CS, intralesional resection with addition of adjuvant treatment, such as cementation, is a widely accepted treatment.<sup>7-10</sup> In true grade 1 CS,

**Table 1.** Patient characteristics

Patient characteristics	n (%)
Eligible patients	126 (100)
Gender	
Male	82 (65)
Female	44 (35)
Location	
Pelvis	54 (43)
Extremity	69 (55)
Appendicular	2 (2)
Grade of the local recurrence	
Grade 1	11 (9)
Grade 2	35 (28)
Grade 3	16 (13)
Dedifferentiated	19 (15)
No histology	17 (14)
Not applicable	28 (22)
Increase in grade from primary to local recurrence	18 (23)
Surgical treatment for local recurrence	
No surgery	40 (32)
Limb salvage	63 (50)
Amputation/hindquarter	23 (18)
Margin in local recurrence surgery	
Wide	21 (17)
Marginal	34 (27)
Intralesional	7 (4)
No surgery	40 (32)
Not reported	14 (11)
Second local recurrence	32/86 (37)
Metastasis prior or at the time of local recurrence	44/126 (35)
Grade 1	0/27 (0)
Grade 2	22/47 (47)
Grade 3	11/29 (38)
Dedifferentiated	11/23 (48)
Patients with metastases during the study time	69 (55)
Mean time from primary operation to local recurrence, mths	28 (2 to 237)
Mean time from first to second local recurrence, mths	33 (0 to 208)
Mean age at the time of local recurrence, yrs	56 (13 to 96)

intralesional curettage gives good local and systemic control, but this is reliant on accurately differentiating grade 1 CS from grade 2 CS preoperatively, as intralesional curettage is not an acceptable treatment for grade 2 CS, due to the high rate of local recurrence (LR) and a decreased survival after LR.<sup>11</sup>

Misdiagnosing the grade may lead to an underestimation of the required margin and thereby increase the risk of LR. In true grade 1 CS, LR has a low impact on survival. We have previously shown that in grade 2 and 3 CS, LR significantly decreased the disease-specific survival (DSS) in competing risk analysis, where synchronous metastases (metastases developed before LR, at the time of LR, or within 90 days after LR) and death due to other causes were considered to be competing events in analyses of the role of LR in DSS.<sup>11</sup> High-grade tumours are easier to diagnose and the best surgical strategy is clearly defined.<sup>11,12</sup>

Wide surgical excision minimizes the possibility of LR, but is often mutilating and sometimes, depending on the location of the tumour, impossible to achieve. A positive margin is a well-documented risk for LR in CS, but in higher grades

the definition for an acceptable wide margin remains a matter for debate. We have previously shown that surgeons should aim for a 4 mm margin to reduce the risk of LR in high grade CS.<sup>11</sup>

The purpose of the current study was to investigate the effect of surgical treatment of locally recurrent chondrosarcoma on local recurrence-free survival (LRFS) and DSS.

## Patients and Methods

This retrospective study included 126 patients, identified from a prospectively maintained database, who had been diagnosed with LR of a chondrosarcoma of the pelvis or a limb bone between 1990 and 2015 at the Royal Orthopaedic Hospital, Birmingham, United Kingdom. There were 44 female patients (35%) and 82 male patients (65%) with a mean age at the time of LR of 56 years (13 to 96). The 126 patients represented 24.3% of the total number of patients with a primary CS (519) who had been treated during this time. All patients were diagnosed and treated at the Royal Orthopaedic Hospital. Those who were primarily treated elsewhere and referred for the management of a recurrence were excluded. Details of the clinical data collected at the time of primary tumour and LR included the site (appendicular, extremity, or pelvis); primary and LR tumour size (in centimetres); type of operation at the time of primary or LR (limb-salvage or amputation); surgical margin achieved at resection of the primary tumour and the LR; grade of the primary tumour and the LR; gender; age; and oncological outcomes, including LRFS and DSS. A minimum two years' follow-up and complete histopathology records were available for all patients included in the study. Resection and LR specimens were examined by specialized bone sarcoma pathologists, for grade and involvement of margins. The highest grade seen on histology was the grade recorded, even when this higher grade consisted of only a small number of cells. The margin was quantified by a specialist bone sarcoma pathologist and classified according to the system described by Enneking et al.<sup>13</sup> Histological biopsies or specimens were not re-reviewed but the original report was respected.

**Statistical analysis.** Descriptive statistics were used to describe demographic data. The Kaplan–Meier method was used to determine LRFS and DSS. Survival rates were calculated from the date of LR to the most recent follow-up, confirmation of a second LR, or death. A Kruskal–Wallis test was used for statistical analysis of means between the groups. Univariable analysis was performed by comparing groups with log-rank test with subsequent multivariable Cox proportional hazard analysis of significant variables to identify predictors of LRFS and DSS. A p-value < 0.05 was considered significant. All statistical analysis was completed using SPSS Statistics 24.0 (IBM Corp., Armonk, New York).

## Results

**Clinical features.** The mean age for patients with synchronous metastases at the time of LR was 61 years (21 to 88). For those without metastases at the time of LR, the mean age was 53 years (13 to 84) (p = 0.004). The mean time from primary surgery to LR was 28 months (2 to 237). The mean follow-up after LR was 45 months (0 to 256). Patient characteristics are summarized in

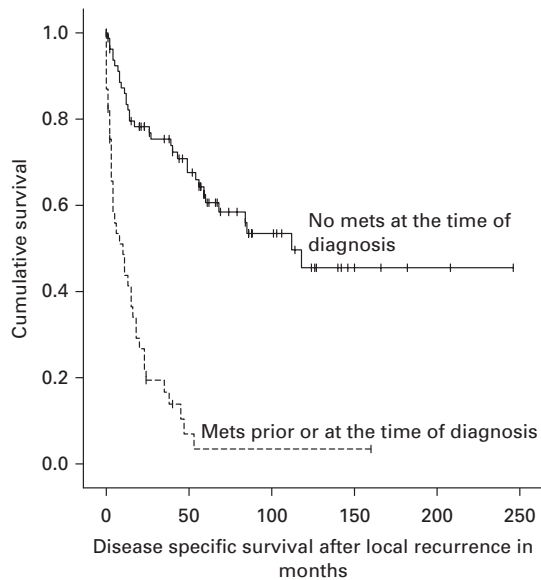


Fig. 1

Disease-specific survival after local recurrence stratified by metastases (mets) prior to or at the time of local recurrence.

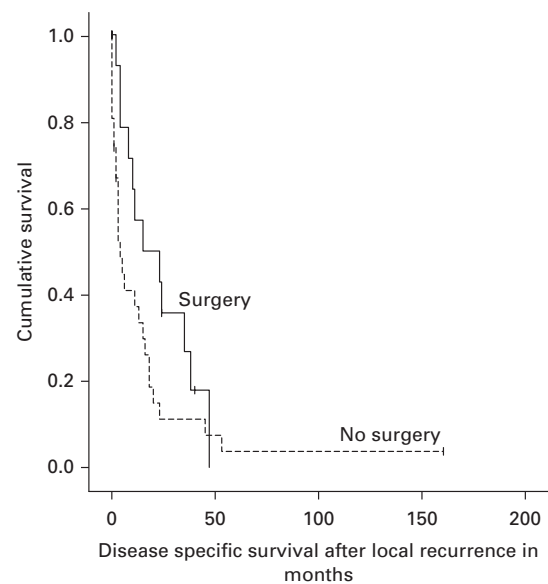


Fig. 2

Disease-specific survival after local recurrence stratified by surgery for local recurrence in patients with metastases.

Table I. The most common sites of the primary tumour were the proximal femur in 28 patients (22.2%), the acetabulum in 24 patients (19.0%), the ilium in 16 patients (12.7%), the distal femur in 15 patients (11.9%), the scapula in eight patients (6.3%), the finger and proximal tibia in six patients (4.8%), the hemipelvis and pubic bone in five patients (4.0%), the proximal humerus in four patients (3.2%), the sacrum and ischial bone in three patients (2.4%), the proximal fibula in two patients (1.6%), and the distal tibia in one patient (0.8%).

Altogether, 44 of the 126 patients (35%) had metastases prior to, or at the time of LR. Metastasis was a significant negative factor for survival. Survival for patients with metastases prior to, or at the time of, LR was 43.7% at one year and 6.9% at five years: 50.0% of patients died within eight months of developing metastases (Fig. 1). Surgical treatment of LR among patients with metastases at the time of or prior to LR does not improve survival ( $p = 0.218$ ) (Fig. 2).

The histological grade of the LR was available for 81 patients (64%). In 18 of these 81 patients (22%), the grade of LR had increased from the original resection specimen. Of 18 grade 1 primary tumours, eight had increased to grade 2 in the LR specimen, three had increased to grade 3, and one had increased to a dedifferentiated (DD) CS. Of 33 grade 2 primary CS, five had increased to grade 3 in the LR specimen and two had increased into DD CS. The grade of LR remained the same in all grade 3 and DD CS. In grade 1 CS primary tumours treated by intralesional curettage, the increase in grade did not have an impact on overall survival ( $p = 0.238$ ).

Of the 126 patients, 40 patients (32%) did not undergo surgery for their LR. In most, due to the presence of metastatic disease prior to, or at the time of, LR, 28 of the 126 patients (22%) underwent amputation (including hindquarter amputation). Of

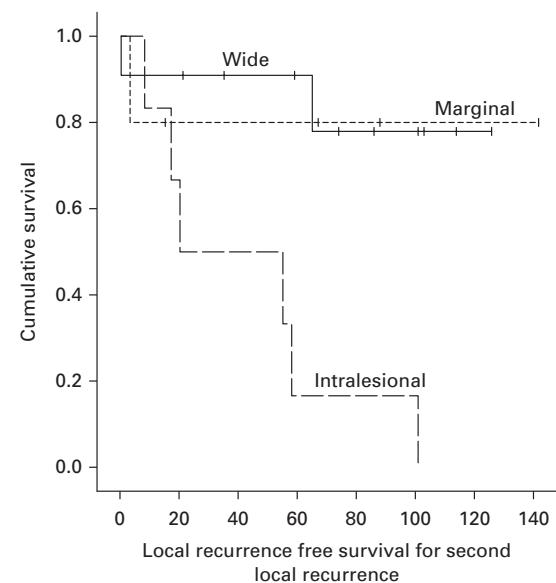


Fig. 3

Local recurrence-free survival stratified by margin.

the 126 patients, 58 patients (46%) had limb salvage or local resection of the LR at the site of a previous amputation. Margin ( $p = 0.251$ ), DSS ( $p = 0.091$ ), and LRFS ( $p = 0.117$ ) were unaffected by the method of surgical management of the LR in terms of limb salvage or limb sacrifice. Surgical margin of the LR resection specimen was recorded in 72 patients (83.7%) and was intralesional in 17 patients (23.6%), marginal in 34 patients (47.2%) and wide in 21 patients (29.2%). A second LR

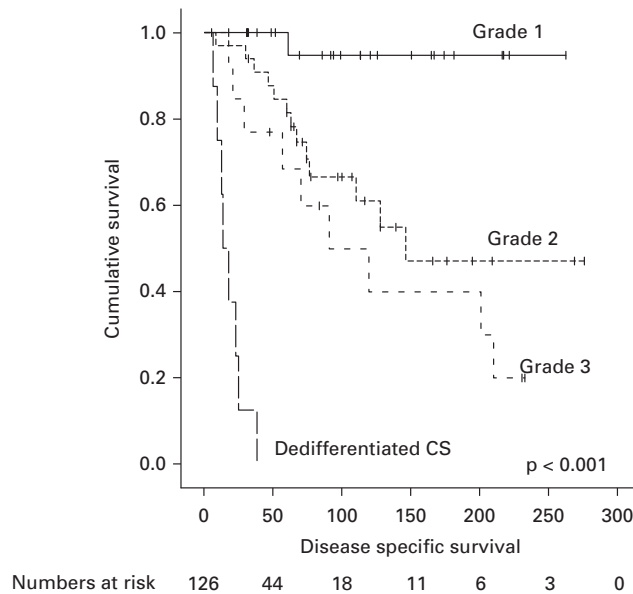


Fig. 4

Disease-specific survival after local recurrence stratified by grade.

**Table II.** Results from univariable analysis for disease-specific survival in patients without metastases prior to, or at the time of, local recurrence

Variable	p-value*
Second local recurrence	0.606
Wide margin	0.044
Metastases	< 0.001
Grade	< 0.001
Gender	0.136
Location (pelvic vs extremity)	0.456
Increase of grade in local recurrence	0.584

\*Kaplan-Meier analysis

was seen in 32 patients (37.2%). The mean time from the first LR to subsequent LR was 33 months (1 to 208). LRFS for the second LR (LRFS) was 65.7% at five years and 42.6% at ten years. A wide margin was a good predictor in LRFS for second LR in univariable analysis when compared with intralesional margin ( $p = 0.002$ ) but marginal margin did not reach statistical significance when compared with intralesional margin ( $p = 0.084$ ) (Fig. 3).

Overall, DSS after LR was 42.1% at five years and 31.2% at ten years. For patients without metastases prior to, or at the time of, LR it was 62.5% and 45.5%, respectively (Fig. 1). In patients without metastases prior to, or at the time of, LR, significant factors affecting DSS after univariable analysis were grade ( $p < 0.001$ ) (Fig. 4), wide margin compared with intralesional margin ( $p = 0.044$ ), wide margin compared with marginal margin ( $p = 0.026$ ), and marginal margin compared with intralesional margin ( $p = 0.046$ ) in resection of the LR (Fig. 5). After multivariable analysis, grade, age at diagnosis of LR, and time from index surgery to LR were significant factors for DSS. These results are summarized in Tables II and III.

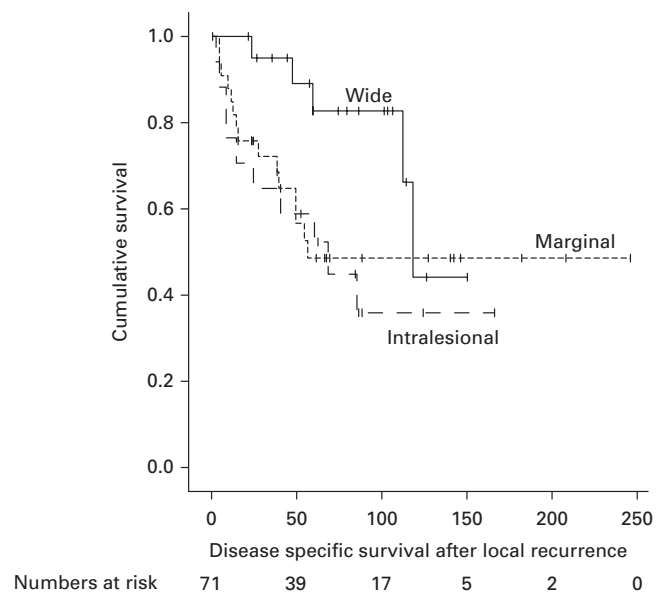


Fig. 5

Disease-specific survival after local recurrence stratified by margin.

**Table III.** Predictors in multivariate analysis for disease-specific survival in patients without metastases prior to, or at the time of, local recurrence

	Hazard ratio	95% confidence interval	p-value*
Dedifferentiated CS	1		
Grade 1 CS	0.003	0.000 to 0.050	0.000
Grade 2 CS	0.018	0.002 to 0.205	0.006
Grade 3 CS	0.23	0.002 to 0.299	0.004
Age at the time of surgery, per year	1.028	1.005 to 1.051	0.018
Time to LR in months, per month	0.942	0.891 to 0.995	0.034
Progression in grade of LR	0.757	0.276 to 2.072	0.587
Location (extremity vs pelvis)	0.710	0.368 to 1.370	0.307

\*Cox regression analysis

CS, chondrosarcoma; LR, local recurrence

## Discussion

Recurrence of CS, whether in the form of local or metastatic disease, adversely affects survival. The aim of treatment of a primary CS is to avoid LR, but in cases of LR, we have shown that for patients without metastases at the time of LR, resection of recurrent disease with wide margins improves both DSS and LRFS, when compared with marginal or intralesional margins. Further surgery may lead to additional morbidity and a higher rate of amputation. Although amputation as a method of treatment of the primary tumour itself does not increase control of systemic or local disease,<sup>11</sup> large resections and reconstructions in the primary operation may reduce the possibility of further limb salvage surgery, thereby increasing the risk of higher amputation or hind-/forequarter amputation.

The definition of wide margin in Enneking's classification system refers to removing the involved part of the bone with a cuff of normal tissue. The metric definition of an acceptable margin has never been accurately defined. The incidence of wide resection margins in our study was considerably lower



than that reported in the literature, being only 29% when compared with 76% in the study from Streitburger et al.<sup>14</sup> However, the survival rates were almost identical, which highlights the difficulty and the discrepancy that exists in defining what constitutes a wide margin or, more importantly, an adequate margin to reduce the risk of LR.<sup>14</sup>

The DSS after LR for all patients was 42.1% at five years and 31.2% at ten years. For patients without metastases prior to, or at the time of, LR, the DSS was 62.5% and 45.5% at five and ten years, respectively. Survival rates are slightly lower than in some studies in the literature,<sup>15,16</sup> but in agreement with other studies.<sup>14,17</sup> In line with current studies in the literature, tumour grade was the most important prognostic factor for patient survival in LRs.<sup>6,12,13,18,19</sup> We found that LR of grade 1 CS was associated with a substantially worse DSS only if the grade of LR had progressed. The difference was not statistically significant, although this may be compounded by the rarity of the event. The role of progression of grade in LR has long been debated.<sup>17,20-22</sup> We have previously shown that the grade of CS should be defined by the highest grade seen in the specimen regardless of how small the area of involvement.<sup>12</sup> We would speculate that higher grade areas seen in the LR are reflective of the difficulty of grading the primary tumour, as small areas of higher grade may be overlooked when analyzing the primary specimen.

The development of metastasis is a poor prognostic indicator; 50% of patients with metastases prior to, or at the time of, LR died within eight months, with most of the rest succumbing to the disease within five years, irrespective of the grade. Despite the potential bias towards more aggressive treatment for patients without disseminated disease, surgery for LR in patients with metastases prior to, or at the time of, LR did not give any statistically significant survival advantage. We would therefore advocate that aggressive mutilating surgery should not be offered to patients in the presence of metastatic disease, unless this is within the context of a palliative approach. The role of metastasectomy for patients with resectable metastases and LR was not investigated in this study but may be considered on a case-by-case basis. However, the development of metastatic disease with LR is suggestive of a more aggressive form of the disease and so caution should be exercised as to the achievement of cure with combined resection.

Primary pelvic CS is notoriously difficult to treat; treatment has a worse outcome than that of extremity CS.<sup>1,18</sup> In accordance with current literature, our results show that late age at onset and shorter disease-free interval are additional factors which adversely affect the outcome after LR.<sup>17</sup> Therefore, the early and accurate detection of LR by frequent follow-up with local imaging is of paramount importance. Whether the frequency and modality of this follow-up should be tailored on an individual patient basis based on the grade, site, size, and margin remains an area of debate. In the absence of such data, regular surveillance in line with national and international guidelines should be advocated.

This study has a number of limitations. First, it is a retrospective study compiled from a prospectively maintained database from a single hospital. Second, margin determinations were recorded from pathology reports rather than re-analyzing

each specimen. Therefore, the data relating to margin is prone to sampling error not only of the margin but also of the grade of the tumour at resection.

In conclusion, aggressive surgical resection with wide margins remains the cornerstone for achieving disease control in patients with locally recurrent CS without metastatic disease, to ensure long-term systemic and local DSS.



### Take home message

- The development of local recurrence (LR) in chondrosarcoma (CS) has a detrimental effect on overall survival, although this is affected by the grade of the original tumour and the grade of the LR.

- Surgery for patients with LR of CS who have previously developed metastases or develop them at the time of the recurrence does not improve overall survival.

- Resection of recurrent disease improves overall survival and disease-specific survival in patients without metastatic disease, only when resection achieves a wide margin.

### Twitter

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#### Author contributions:

M. K. Laitinen: Study conception and design, Collected and analyzed the data, Prepared the manuscript.  
M. C. Parry: Study conception and design, Prepared the manuscript.  
L-R. Le Nail: Collected and analyzed the data, Prepared the manuscript.  
C. H. Wigley: Collected and analyzed the data, Prepared the manuscript.  
J. D. Stevenson: Prepared the manuscript.  
L. M. Jeys: Study conception and design, Prepared the manuscript.

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